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Clinical letter

Sudden cardiac death in a patient with LGI1 antibody-associated encephalitis

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1. Introduction

Anti-leucine-rich glioma-inactivated 1 limbic encephalitis (LGI1-LE) is one of the clinical syndromes associated with antibodies to voltage-gated potassium channels (VGKCs) [1]. In addition to the common LE symptoms such as cognitive impairment, psychiatric disturbances and seizures, patients with LGI1-LE manifest hyponatremia, and faciobrachial dystonic seizures (FBDS) in about 50% of cases. MRI abnormalities usually involve the medial temporal lobe and basal ganglia. LE typically affects middle-aged patients with a 2:1 male to female ratio and is rarely associated with cancer [1]. Although long-term outcomes may vary, patients usually demonstrate a good response to early immunotherapy, with seizure suppression and a positive effect on cognition [2].

2. Case description

A 55-year-old male, with smoking habit, developed mood changes and brief episodes lasting a few seconds characterized by involuntary movements and tingling of the right hand followed by contraction of the right arm and leg, mouth deviation and, occasionally, loss of consciousness and falling, that became more frequent (i.e. up to 4–5 per day) over time. Concurrently, he complained of memory loss, depression and sleep disturbances with frequent awakenings. His condition deteriorated over the next 5 months and he had to stop working and driving. He was hospitalized in December 2010 after a severe seizure accompanied by screaming, extension of the neck, diffuse tonic contraction of the body and breathing difficulty. At admission, he was partially oriented, disinhibited and with a depressed mood. He had frequent "jerks" in the face (grimaces with mouth deviation to the right, and right eye winking) and arms (rapid abduction of the right shoulder), suggestive of FBDS. At the time of neuropsychological assessment, he was partially autonomous in activities of daily living. He alternated phases of optimal execution and adequate speech/behavior with transient phases of mental rigidity, hallucinations, confabulations and poor insight. The result was a multimodal cognitive impairment affecting attention, executive functions, memory and language. Apathy, anxiety and depression were reported on HADS questionnaire. Awake EEG showed rare spike-wave complexes in the left fronto-temporal regions. EEG recording during sleep showed diffuse spike-wave bursts with a tendency to become periodical, sometimes associated with ictal activity and clinical manifestation. We recorded an episode

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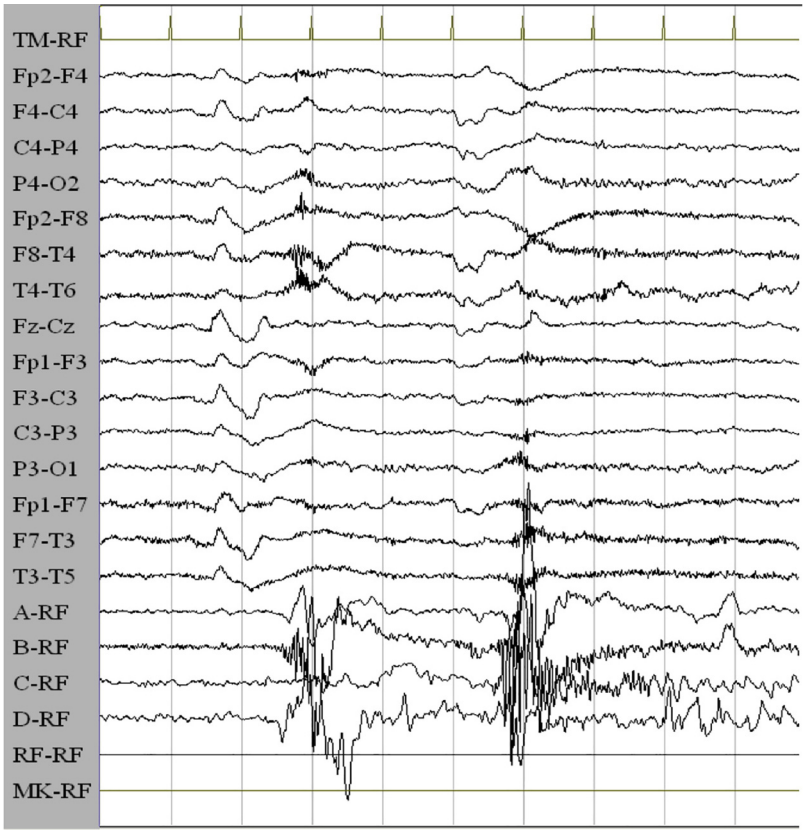

Fig. 1. EEG (sens 10 mV/mm, TC 0.10 s, HF 30.0 Hz) showed diffuse spike-wave complexes becoming periodical, sometimes associated with ictal activity (flattening of the left fronto-temporal activity followed by tonic slow deflection of the left fronto-central) and clinical changes (faciobrachial dystonic seizures). (a: left orbicularis oris muscle; b: right orbicularis oris muscle; c: left deltoid muscle; d: right deltoid muscle).

characterized by flattening of the left fronto-temporal activity followed by tonic slow deflection of the left fronto-central activity lasting about 10–15 seconds, during which the patient showed a grimace of the right side of the face and a jerk of the right arm (Fig. 1). A MRI scan obtained six months after the onset of symptoms showed a mild enlargement of the left amygdala and hippocampus with signal hyperintensity in FLAIR, accompanied by a small altered hippocampal area of 4 mm characterized by signal hyperintensity in T2 and FLAIR, and hypointensity in T1 without enhancement. CSF findings were unremarkable, except for the presence of rare oligoclonal bands. CT scans of chest, abdomen and pelvis were normal. We treated the patient with levetiracetam associated with oxcarbazepine, lorazepam and clonazepam, obtaining partial control of the seizures.

Some days after discharge, the patient's wife witnessed a seizure characterized by screaming, neck extension and limb clonic contractions, followed by prolonged apnea and cardiac arrest. The patient died within approximately ten minutes from the onset of seizure, before reaching the hospital. Arrhythmia was not documented. A full body post-mortem examination was performed. The serological work-up for suspected autoimmune encephalitis, which arrived post-mortem, revealed positivity for LGI1-IgG against VGKC complex (260 pM).

Pathological findings. There were inter-fibrillar aggregates, mainly of granulocytes, suggestive of myocardial ischemia in the territory of the descendant anterior coronary artery (i.e., anterior wall of the left ventricle and interventricular sept), with associated mild, focal, predominantly perivascular, myocardial sclerosis (Fig. 2). Gross inspection excluded the presence of significant coronary obstructive disease. Brain microscopic examination revealed lymphocytic infiltrates with both perivascular ("perivascular cuffing") and interstitial distribution in the amygdala, hippocampus, striatum, and basal forebrain, with moderate reactive astrocytosis and mild neuronal loss in the hippocampus. Perivascular lymphocytes were predominantly CD20+, whereas, in contrast, the majority of those infiltrating the nervous tissue were CD8+. The final diagnosis was LGI1-LE, with myocardial ischemia as cause of death.

3. Discussion

At the time of clinical evaluation, LGI1-LE was an emerging syndrome. In the present case, the diagnosis was uncertain in the early stage and the initial apparent positive response to anti-epileptic drugs contributed to the early patient dismissal. Unfortunately, he unexpectedly died before the results of serological assessments were obtained.

Cardiac clinical manifestations in epilepsy, especially heart rhythm alterations, are well known, and evidence suggesting an ischemic damage, particularly in drug-resistant patients, has also been gathered. Overall, myocardial infarction is rarely described following seizures, although it is probably underreported. Myocardial ischemic events related to epilepsy might be due to vasoconstriction of the coronary arteries secondary to the release of catecholamines induced by the seizures (Supplementary material 1). To our knowledge, this is the first case of histologically documented sudden cardiac death (SCD) in LGI1-LE due to myocardial ischemia with normal coronary arteries.

In people with epilepsy, SCD and sudden unexpected death in epilepsy (SUDEP) are partially overlapping disease entities since cardiovascular disease rather than epilepsy is the main determinant of ventricular arrhythmias [3]. However, in the present case, the lack of evidence of coronary artery disease points to a vasospasm or an arrhythmia triggered by the seizure as the cause of myocardial infarction. According to the recent classification of SUDEP, the cause of death should be classified as Definite SUDEP Plus Comorbidity, given the concomitant, although not independent condition (i.e. the myocardial infarction), which contributed to death [4].

4. Conclusion

SCD is a possible occurrence in LE. We documented with cardiac

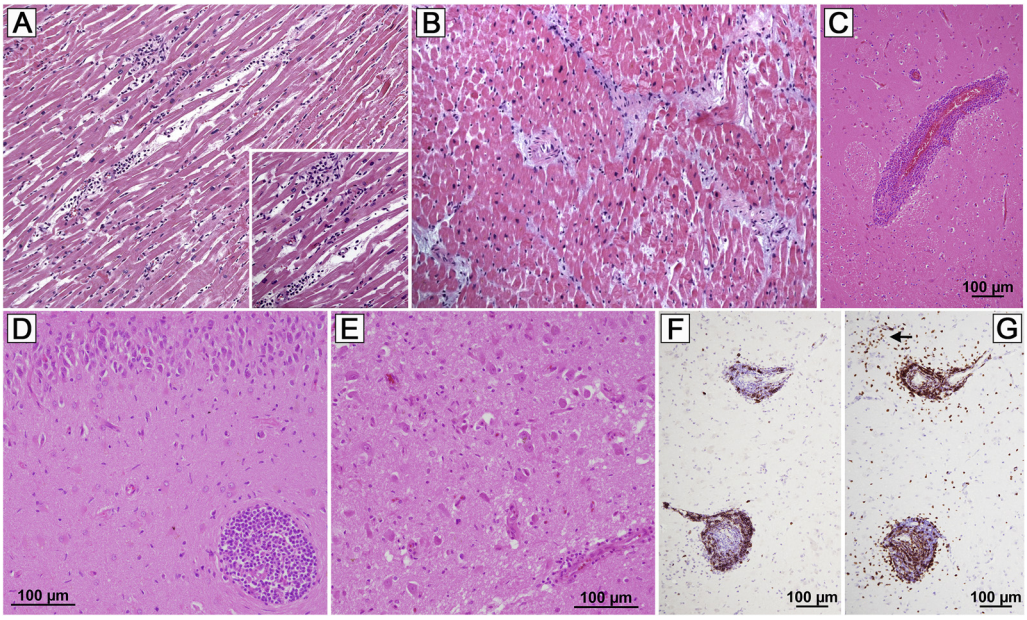

Fig. 2. Histopathological findings. *Myocardium*: (A) inter-fibrillar aggregates of granulocytes (a detail at higher magnification is shown in the low right corner), and (B) perivascular myocardiosclerosis (B). *Brain*: (C) "perivascular cuffing" in the striatum, (D, E) neuronal loss and reactive gliosis in the hippocampus cornu ammonis sector 4 and 1, (F) perivascular CD20 + lymphocites and (G) perivascular and intraparenchymal (black arrow) CD8 + lymphocites (G).
Sections A-E: hematoxylin and eosin staining; F: immunochemistry for CD20 (L26, Dako, Denmark); G: immunochemistry for CD8 (CD8/144B, Dako, Denmark).

histology a case of SCD caused by myocardial ischemia, a condition likely underreported in LE. The risk of SCD in LE should be kept in mind, particularly in patients with drug-resistant seizures, and immunotherapy not be delayed until antibody tests are concluded in any case with suspected autoimmune epilepsy [2]. Indeed, our case suggests that early immunotherapy not only favours cognitive outcomes, but may also prevent premature death.

Declarations of interest

None.

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